Roles of alternative splicing in the functional properties of inner ear-specific KCNQ4 channels.

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Authors: Tonghui Xu, Liping Nie, Yi Zhang, Jiling Mo, Weihong Feng, Dongguang Wei, Evgueni Petrov, Lilian E Calisto, Bechara Kachar, Kirk W Beisel, Ana E Vazquez, Ebenezer N Yamoah

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Public Summary:

Scientific Abstract:
The function of the KCNQ4 channel in the auditory setting is crucial to hearing, underpinned by the finding that mutations of the channel result in an autosomal dominant form of nonsyndromic progressive high frequency hearing loss. The precise function of KCNQ4 in the inner ear has not been established. However, recently we demonstrated that there is differential expression among four splice variants of KCNQ4 (KCNQ4_v1-v4) along the tonotopic axis of the cochlea. Alternative splicing specifies the outcome of functional channels by modifying the amino acid sequences within the C terminus at a site designated as the membrane proximal region. We show that variations within the C terminus of splice variants produce profound differences in the voltage-dependent phenotype and functional expression of the channel. KCNQ4_v4 lacks exons 9-11, resulting in deletion of 54 amino acid residues adjacent to the S6 domain compared with KCNQ4_v1. Consequently, the voltage-dependent activation of KCNQ4_v4 is shifted leftward by approximately 20 mV, and the number of functional channels is increased severalfold compared with KCNQ4_v1. The properties of KCNQ4_v2 and KCNQ4_v3 fall between KCNQ4_v1 and KCNQ4_v4. Because of variations in the calmodulin binding domains of the splice variants, the channels are differentially modulated by calmodulin. Co-expression of these splice variants yielded current magnitudes suggesting that the channels are composed of heterotetramers. Indeed, a dominant negative mutant of KCNQ4_v1 cripples the currents of the entire KCNQ4 channel family. Furthermore, the dominant negative KCNQ4 mutant stifles the activity of KCNQ2-5, raising the possibility of a global disruption of KCNQ channel activity and the ensuing auditory phenotype.